THE GENETICS OF INHERITED AND ACQUIRED MYOPATHY (2017)

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OVERVIEW

Myopathic disorders are composed of a heterogeneous group of muscle diseases, traditionally classified into inherited versus acquired myopathies, and present with signs and symptoms of weakness, but are often further characterized by clinical features unique to the myopathy. Inherited myopathies are caused by genetic defects in the contractile apparatus of the muscle while muscular dystrophies are a result of genetic defects in the muscle membrane or supporting proteins. Acquired myopathies are commonly represented by idiopathic inflammatory myopathies; several recent studies have indicated that these inflammatory myopathies may be caused by certain triggers, which may lead to immune activation in genetically susceptible individuals. This review will highlight the key clinical features and genetic abnormalities involved in the different categories of inherited myopathies, muscular dystrophies, and acquired myopathies, that an accurate diagnosis and management are contingent upon.

MUSCULAR DYSTROPHIES

Myotonic dystrophy type 1: Dystrophica myotonica (DM1) (also known as Steinert's disease) is the most common muscular dystrophy in adults. DM1 is caused by an expansion of a trinucleotide CTG repeat in the DMPK gene (>34 repeats is abnormal).[1] It is characterized as a multisystemic disorder that affects both skeletal and smooth muscle, as well as the heart, eyes, endocrine system and central nervous system. In classic DM1 (CTG repeats of ~100-1000), the clinical characteristics include muscle weakness and wasting, myotonia (delayed relaxation of muscle contraction), frontal balding, cataracts, cardiac conduction abnormalities, endocrine disorders (thyroid, diabetes, etc), and cognitive impairment. Patients may become physically disabled and have a shortened life span. In mild DM1 (CTG repeats of 50 ~ 150), patients may clinically present with mild myotonia and cataracts, yet have a normal life span. Congenital DM1 (CTG repeats >1000) is characterized by neonatal weakness, hypotonia, respiratory insufficiency, intellectual disability and often early death.
It is inherited in an autosomal dominant manner, with an anticipation effect due to the unstable repeats that may expand during meiosis, resulting in a risk of successive generations having an increase in disease severity and an earlier age of onset.

Myotonic dystrophy type 2 is an autosomal dominant disorder caused by a CCTG repeat expansion in the CNBP (ZNF9) gene.[2] The CCTG repeats in expanded alleles range from 75 to more than 11,000, with a mean of 5,000 repeats. Clinically, patients commonly have myotonia accompanied with varying muscle symptoms of pain, stiffness or weakness. Cataracts, cardiac conduction and endocrine abnormalities are less common, but may occur.

Facioscapulohumeral muscular dystrophy (FSHD) typically presents before the age of 20 years with clinical features of weakness of facial muscles, stabilizers of the scapular (scapular winging), and foot dorsiflexors. It is inherited in autosomal dominant manner and likely caused by inappropriate expression of the double homeobox-containing gene DUX 4 in muscle cells, which lies in the macrosatellite repeat D4Z4 on chromosome 4q35 (normal 11-100 repeats). FSHD1 (accounts for approximately 95% of FSHD) is caused by shortening of the D4Z4 allele (1-10 repeats), resulting in chromatin relaxation at the D4Z4 locus and DUX4 promoter and in turn depression of DUX4. In FSHD2 (approximately 5% of FSHD), individuals show a chromatin relaxation at D4Z4 (without having a D4Z4 contraction), but instead have a mutation in SMCHD1 (and DUX4 permissive allele)[3]. FSHD1 and FSHD2 are clinically indistinguishable.

Oculopharyngeal muscular dystrophy (OPMD) is characterized by late-onset, selective involvement of muscles of the eyelid and pharynx resulting in eyelid ptosis and dysphagia, usually manifesting around the fifth decade. Disease progression is slow and is accompanied by proximal limb weakness, gradual limitation of extraocular movements, and voice changes with a hypernasal quality.

It is inherited in either an autosomal dominant or autosomal recessive manner; caused by an expansion of a GCN trinucleotide repeat in the first exon of PABPN1 (normal is 10 GCN repeats). Autosomal dominant alleles range in size from 12-17 GCN repeats, while autosomal recessive alleles have 11 GCN repeats. The GCN repeat in PABPN1 is mitotically and meiotically stable; therefore, clinical anticipation is not observed.

In the US, the majority of affected individuals are of French-Canadian, Jewish Ashkenazi, or Spanish American (from New Mexico, Texas or California) backgrounds.[4]

Dystrophinopathies are a spectrum of muscle diseases that are inherited in an X-linked manner and caused by pathogenic variants in the DMD gene which encodes the protein dystrophin.

Duchenne muscular dystrophy is the most common form of muscular dystrophy; it classically presents in early childhood with delayed motor milestones, proximal weakness and a waddling gait. Due to rapid progression of weakness, most children are wheelchair dependent by the age of 13 years and have associated cardiomyopathy and respiratory insufficiency, resulting in death by the third decade.

Becker muscular dystrophy is characterized by later onset proximal skeletal muscle weakness; some patients may remain ambulatory in their 20s. Mean age of death is mid-40s with dilated cardiomyopathy a major cause of morbidity and mortality in these patients.

Females heterozygous for a pathogenic variant in DMD are at increased risk of a dilated cardiomyopathy and should be routinely followed by a cardiologist.

Some patients may have a pathogenic variant in DMD gene resulting a mild phenotype with a clinical spectrum varying from asymptomatic hyperCKemia (elevation in creatine phosphokinase levels), muscle cramps and myoglobinuria or DMD-associated dilated cardiomyopathy without limb muscle weakness.[4-6]

Emery-Dreifuss Muscular Dystrophy (EDMD) is clinically characterized by a triad of early childhood joint contractures, slowly progressive muscle weakness and atrophy (initially affecting the humero-peroneal distribution with progression to involvement of the scapular and pelvic girdle muscles), and cardiac abnormalities (arrhythmias or congestive heart failure). Age of onset clinically varies from early-onset with severe presentation in childhood to late-onset with slow progression in adulthood. Pathogenic variants found in three genes are known to cause EDMD: EMD (encoding emerin, accounting for ~60% of X-linked) and FHL1 (encoding FHL1, accounting for ~ 10% of X-linked) cause X-linked EDMD; and LMNA (encoding lamin A and C) causes autosomal dominant EDMD and autosomal recessive EDMD.[7]

LIMG GIRDLE MUSCULAR DYSTROPHIES (TABLE 1)

The limb-girdle muscular dystrophies (LGMD) are a genetically and clinically heterogeneous group of inherited muscle disorders that are defined by predominantly proximal distribution of weakness, typically first affecting the hip and shoulder girdle muscles. The genetically distinct subtypes have defined the classification of LGMDs with the nomenclature designated by a number for the mode of inheritance (LGMD1 for autosomal dominant and LGMD2 for autosomal recessive) and a letter for the order of discovery (1A was found before 1B). With the advancements in next generation sequencing approaches, new LGMD genes have recently been discovered, making the genetic classification complex as there are now thirty-one LGMD loci identified [eight autosomal dominant (LGMD1 A-H, table 1) and 23 autosomal recessive (LGMD2 A-W, table 1)]. The list of genes to be tested is too large for the gene-by-gene approach, thus recognition of certain clinical features associated with the different types of LGMDs may help aid the approach to the diagnosis. The autosomal dominant and more common autosomal recessive LGMD subtypes with emphasis on their key characteristics will be reviewed.[6,8,9]

Autosomal Dominant LGMD

The autosomal dominant forms of LGMD (designated LGMD1) typically present with an adult-onset, have milder weakness with more gradual progression, and less of an elevation in creatine kinase (CK) levels in comparison to the autosomal recessive subtypes. They are less frequent, representing less than 10% of all LGMDs.[10]

LGMD1A is caused by mutations in the gene-encoding myotilin, a Z-disk associated protein. Patients present with proximal weakness followed by distal weakness and may have a nasal, dysarthric speech. Muscle biopsies reveal basophilic rimmed vacuoles and Z-line streaming on electron microscopy.[11] The same gene mutation has been associated with histopathological changes consistent with myofibrillar myopathy and more distal predominant weakness, myalgias and stiffness.[12]

LGMD1B is due to mutations in the LMNA gene encoding lamin A/C, a nuclear protein with roles ranging from nuclear membrane maintenance to gene regulation. Patients may develop early joint contractures (elbows, heel cords, neck) and proximal leg weakness with age-dependent cardiac conduction abnormalities more commonly than dilated cardiomyopathy and a risk for sudden death 20-30 years later. Mutations in the same gene may present with a variety of different phenotypes including: Emery-Dreifuss muscular dystrophy (EDMD), axonal Charcot-Marie-Tooth disease, congenital muscular dystrophy, Hutchinson-Gilford progeria syndrome, lipodystrophy and dilated cardiomyopathy.[13]

LGMD1C is due to mutations in the CAV3 gene encoding caveolin-3, a muscle membrane protein and the principal component of caveolae membrane. Patients can present in the first decade of life and may have mild proximal weakness, calf hypertrophy, and muscle cramps after exercise. The presence of rippling waves of muscle contraction associated with symptoms of stiffness or weakness may be a manifesting sign ("rippling muscle disease").

LGMD1D is due to mutations in the DNAJB6 gene leading to insufficient clearance of misfolded proteins. Proximal leg weakness may be the initial presentation, though distal weakness has also been described. Age of onset ranges from 20-50 years and many patients remain ambulatory into their sixties. Muscle histology may show rimmed vacuoles.[14]

LGMD1E is considered a disorder designated under the term myofibrillar myopathy caused by a mutation in the gene for desmin, an intermediate filament that spans from the sarcolemma to the sarcomere and to the nucleus. Proximal muscle weakness may present in the 2nd or 3rd decade and has been associated with dilated cardiomyopathy, conduction defects and mild CK elevation. Perinuclear or subsarcolemmal granulofilamentous inclusions have been described on muscle biopsy.[15]

LGMD1F is caused by a mutation in the transportin 3 (TNPO3) gene and has a severe phenotype in those presenting in the early teens yet a slower progression in the adult onset patients. Some patients have been reported to have prominent atrophy of proximal leg muscles, dysphagia, arachnodactyly and respiratory insufficiency.

LGMD1G is caused by a defect in the RNA processing protein HNRPDL. Patients have been reported to present with late-onset, progress slowly, and have associated progressive limitation of finger and toe flexion.

LGMD1H has been described in a family from Italy, mapped on chromosome 3p23-p25.1, and presents with slowly progressive proximal weakness with onset during the fourth-fifth decades.

Autosomal Recessive LGMD

The autosomal recessive forms of LGMD (designated LGMD2) are more common with a prevalence of 1:15,000;[16] some differences are noted amongst countries depending on the carrier distribution and degree of consanguinity.[10]

LGMD2A is due to mutations in CAPN3, encoding calpain 3, a protease modulated by calcium ions that binds to titin. It represents the most frequent LGMD in most geographic regions (accounts from 9-40% of cases).[17-19] Majority of patients have onset of proximal limb-girdle weakness before 20 years of age, CK elevations of 5-10 times the normal range, and may have scapular winging. Muscle biopsies may show lobulated fibers on oxidative enzyme stains.[20]

LGMD2B is caused by mutations in DYSF, encoding dysferlin, a transmembrane protein involved in calcium-mediated sarcolemma resealing. It is the second most frequent LGMD2 form in many countries,[21] especially noted in Asian populations and in regions around the Mediterranean Sea. Patients typically present in early adulthood, between ages of 15-30 years, with weakness beginning in the legs and many with distal leg weakness

(a purely distal form with severe calf wasting appears as Miyoshi myopathy). CK may be more than 10 times normal in dysferlinopathies. Immunohistochemical analysis may detect dysferlin deficiency although should be interpreted with caution given the presence of secondary protein-staining changes.[22]

LGMD2C-D-E-F are caused by mutations in the genes encoding the four members of the sarcoglycan complex: alpha, beta, gamma, and delta (cause 2D, 2E, 2C, and 2F, respectively). They are N-glycosylated transmembrane proteins and components of the dystrophin-associated glycoprotein complex. All have childhood onset, similar phenotypes to Duchenne/Becker dystrophies with cardiac and respiratory involvement. Muscle biopsy reveals reduced protein expression of alpha, beta, gamma or delta sarcoglycan.

LGMD2I, 2K, 2M, 2N, 2O, 2P are dystroglycanopathies resulting from mutations in six genes (FKRP, POMT1, FKTN, POMT2, POMGnT1, DAG1, respectively) that reduce dystroglycan glycosylation and result in a wide range of phenotypes.

LGMD2I: Mutations in FKRP, fukutin-related protein, account for approximately 10-15% of LGMD patients, especially noted in those of Northern European heritage.[23] Age of onset varies, commonly before the third decade with clinical features of calf hypertrophy, lumbar lordosis and tongue hypertrophy. Patients may have early involvement of cardiac and respiratory dysfunction; thus mimicking Duchenne muscular dystrophy.

LGMD types 2K, M, N, O, and P are rare, typically present early in childhood as congenital muscular dystrophies or muscle-eye-brain disease.

LGMD2J is caused by mutations in the TTN gene encoding for titin, the largest protein of the human genome that forms a continuous filament spanning half the sarcomere from the Z-disc to the M-band and contains binding sites for calpain 3. Patients may develop a late-onset, distal tibial muscular dystrophy, noted in Finland or may have more severe cardiac or muscular phenotypes.

LGMD2L is due to mutations in the anoctamin-5 gene (ANO5) and is one of the most frequent types in Northern Europe, accounting for 10-20% of LGMD cases.[24] Anoctamins are a family of calcium-activated chloride channels. Onset is generally in adulthood and patients may have prominent, asymmetric quadriceps atrophy with CK elevations from 5-20x normal. Cardiac or respiratory dysfunction has not been reported.

LGMD2V subtype has been proposed as an occasional form of LGMD that is derived from mild mutations of the acid alpha-glucosidase (GAA) gene. Deficiency in GAA causes glycogen storage disease type 2 with a broad clinical spectrum (Pompe disease) from a severe form presenting in infancy, to a late-onset Pompe disease, presenting from the 2nd to as late as the 7th decade and resulting in progressive proximal weakness (as seen in LGMDs) and respiratory insufficiency.[25]

OTHER INHERITED MYOPATHIES

Inclusion body myopathy with Paget Disease of Bone (PDB) and/or Frontotemporal Dementia (IBMPFD) is clinically characterized by adult-onset proximal and distal limb weakness (resembling limb-girdle muscular dystrophies), accompanied by PDB (focal areas of increased bone turnover, mean age 42 years) and early-onset frontotemporal dementia (mean age 55 years). Respiratory insufficiency and cardiomyopathy have been observed in later stages. IBMPFD is inherited in an autosomal dominant manner and is caused by a mutation in the VCP gene, encoding valosin-containing protein.[26,27]

DISTAL MYOPATHIES (TABLE 2)

Distal myopathies are composed of heterogeneous group of distal myopathies and muscular dystrophies. The genetic classification is shown in (Table 2). Age of onset is variable, typically later in life; many with symptom manifestation in adulthood and a predilection to initially affect particular distal muscle groups, as characterized in Table 2.[28-31]

GNE-related myopathy, also known as hereditary inclusion body myopathy 2, is characterized by slowly progressive distal weakness that starts in young adulthood (third decade), initially affecting the tibialis anterior muscles, resulting in a foot drop and gait difficulty, with subsequent involvement of hand and thigh muscles; yet is quadriceps sparing. Within 20 years of onset of weakness, many patients require a wheelchair for mobility. GNE-

related myopathy in inherited in an autosomal recessive fashion, resulting from mutations in the GNE gene, encoding the bifunctional enzyme UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase. It was likely first recognized in Japan, reported by Nonaka in 1981, as an autosomal recessive distal myopathy with rimmed vacuoles seen on muscle biopsy. Since then, several individuals, mostly of Iranian Jewish or Japanese descent have been described.

Several therapies are under investigation in clinical trials for GNE-myopathy including replacing sialic acid or its metabolites.[32-34]

CONGENITAL MYOPATHIES (TABLE 3)

Congenital myopathies typically present in childhood with hypotonia, delayed motor milestones, feeding and respiratory difficulties. Milder presentations occur later in life manifesting with complications such as scoliosis, contractures, and respiratory insufficiency. The spectrum of phenotypic severity varies widely. Patients may have generalized or proximal muscle weakness, reduced muscle bulk, dysmorphic facial features (elongated face, high arched palate), pectus carinatum, scoliosis. While respiratory muscles are usually involved, cardiac involvement is rare.[31,35,36]

CONGENITAL MUSCULAR DYSTROPHIES (TABLE 4)

Congenital Muscular Dystrophies (CMDs) usually present in the first year of life with clinical features of hypotonia and weakness, swallowing difficulty, respiratory insufficiency and arthrogryposis. Weakness may be static or slowly progressive and may be accompanied by hypertrophy of tongue and limb muscles, scoliosis and contractures with age. CMDs are caused by defects in proteins of the sarcolemmal membrane or its supporting structures and may be expressed in the central nervous system, resulting in brain and eye abnormalities. Most are inherited in an autosomal recessive manner.[31,37,38]

MITOCHONDRIAL MYOPATHIES

Mitochondrial myopathies are a heterogeneous group of disorders that result from a dysfunction of the mitochondrial respiratory chain and are caused by mutation of genes encoded by either nuclear DNA or mitochondrial DNA. Some mitochondrial disorders only affect a single organ (for example, the eye in Leber hereditary optic neuropathy), while many involve multiple organs systems with prominent neurologic and myopathic features including, (but are not limited to): Kearns-Sayre syndrome (KSS), chronic progressive external ophthalmoplegia (CPEO), myoclonic epilepsy with ragged-red fibers (MERRF), myoclonic epilepsy myopathy sensory ataxia (MEMSA), and mitochondrial encephalomyopathy with lactic-acidosis and stroke-like episodes (MELAS), myo-neuro-gastro-encephalopathy (MNGIE), autosomal recessive cardiomyopathy and ophthalmoplegia (ARCO), and Leigh syndrome.[39]

ACQUIRED MYOPATHIES

Acquired myopathies encompass a phenotypically variable group of rare diseases and are commonly represented by idiopathic inflammatory myopathies (IIM). These myopathies include polymyositis, dermatomyositis, immune-mediated necrotizing myopathy and sporadic inclusion body myositis. While polymyositis, dermatomyositis and immune-mediated necrotizing myopathy are characterized as autoimmune disorders; inclusion body myositis is thought to have features of both autoimmunity and muscle fiber degeneration. The causes of the various forms of myositis are still unknown. Several studies indicate environmental exposure to such triggers as infections agents, toxins (usually drugs), ultraviolet radiation, or combinations of these mechanisms may lead to immune activation in genetically susceptible individuals. Recent advances have been made in our understanding of the genetics of IIM.

Two human leukocyte antigen (HLA) imputation studies have confirmed a strong association with the 8.1 ancestral haplotype in clinical subgroups of myositis and suggest multiple independent associations on this haplotype. A large genetic study revealed multiple non-HLA associations in IIM patients, that also overlap with risk variants reported in other seropositive autoimmune diseases. Candidate gene studies in the Japanese and Han Chinese IIM patients have replicated previous IIM associations in the Caucasian population suggesting a common etiology between ethnicities. Future approaches planned, such as sequencing and trans-ethnic meta analysis, and utilizing international biorepositories will help advance our understanding of the genetics implicated in IIM.[40,41]

Table 1: Limb Girdle Muscular Dystrophies (LGMD)				
Autosomal Dominant Subtypes				
Subtype	**Gene**	**Protein**	**Clinical features** Unique to subtype	**CK level** (times normal)
LGMD1A	TTID	Myotilin	Dysarthria	3-4x
LGMD1B	LMNA	Lamin A/C	Joint contractures Cardiomyopathy	1-6x
LGMD1C	CAV3	Caveolin 3	Rippling muscle	10x
LGMD1D	DNAJB6	DNAJ/Hsp40 homolog	Onset 25-50 yrs Lower legs more affected	1-10x
LGMD1E	DES	Desmin	Cardiomyopathy	5-10x
LGMD1F	TNPO3	Transportin 3	Anticipation, More severe phenotype in teens	1-3x
LGMD1G	HNRPDL	Heterogeneous nuclear Ribonucleoprotein D-like protein	Finger flexion limitation	1-9x
LGMD1H	-	-	-	1-10x
Autosomal Recessive Subtypes				
Subtype	**Gene**	**Protein**	**Clinical features** Unique to subtype	**CK level** (times normal)
LGMD2A	CAPN3	Calpain 3	Hip adductor weakness, Scapular winging, Contractures	3-20x
LGMD2B	DYSF	Dysferlin	Distal leg weakness	5-40x
LGMD2C	SGCG	γ-Sarcoglycan	Duchenne/Becker phenotype	10-70x
LGMD2D	SGCA	α-Sarcoglycan	Duchenne/Becker phenotype	10-70x
LGMD2E	SGCB	β-Sarcoglycan	Duchenne/Becker phenotype	10-70x
LGMD2F	SGCD	δ-Sarcoglycan	Duchenne/Becker phenotype	10-70x
LGMD2G	TCAP	Telethonin	Brazilian	10x
LGMD2H	TRIM32	Tripartite motif containing 32	Hutterite	10x
LGMD2I	FKRP	Fukutin-related protein	Calf hypertrophy, Cardiac + Respiratory	10-20x
LGMD2J	TTN	Titin	Finnish, Severe weakness, 1st -3rd decade of life	10-40x

LGMD2K	POMT1	Protein-O-mannosyl transferase 1	Mental retardation, Childhood onset	10-40x
LGMD2L	ANO5	Anoctamin 5	Quadriceps atrophy, Asymmetric, Northern European	1-15x
LGMD2M	FKTN	Fukutin	Early childhood	10-70x
LGMD2N	POMT2	Protein-O-mannosyl transferase 2	Muscle-eye-brain disease, Early childhood	5-15x
LGMD2O	POMGnT1	Protein-O-linked mannose beta 1,2N-acetylglucosaminyl transferase	Muscle-eye-brain disease, Late childhood	2-10x
LGMD2P	DAG1	Dystroglycan	Mental retardation, Early childhood	20x
LGMD2Q	PLEC1	Plectin	Turkish family, Early childhood	10-50x
LGMD2R	DES	Desmin	Turkish family, Young adulthood, Conduction block	1x
LGMD2S	TRAPPC11	Transport protein particle complex 11	Syrian: impaired ambulation Hutterite: chorea, ataxia	9-16x
LGMD2T	GMPPB	GDP-mannose pyrophosphorylase B	Early childhood, Mild intellectual delay, Seizures	
LGMD2U	ISPD	Isoprenoid synthase domain containing	Teenage years – loss of ambulation, Cardiac + Respiratory	6-50x
LGMD2V	GAA	Alpha-1,4-glucosidase	Respiratory insufficiency, Scapular winging	1-20x
LGMD2W	LIMS2	Lim and senescent cell antigen-like domain 2	Calf hypertrophy, Macroglossia, Cardiomyopathy	-

Table 2: Distal Myopathies			
Type	**Gene**	**Age of onset**	**Clinical features** Initial affected muscle group
Late Onset Type I (Welander)	Unknown	Late adulthood	Finger and wrist extensors
Late Onset Type II (Markesbury-Griggs Udd)	Titin	Late adulthood	Anterior compartment of legs
Early Onset Type I (Nonaka, GNE-myopathy)	Bifunctional enzyme GNE	Early adulthood	Anterior compartment of legs
Early Onset Type II (Miyoshi)	Dysferlin	Early adulthood	Posterior compartment of legs
Early Onset Type III (Laing)	Slow myosin heavy chain (MYH7)	Early adulthood	Anterior compartment of legs, Neck flexors
Distal dystrophy with vocal cord and pharyngeal weakness	Unknown	Late adulthood	Anterior compartment of legs, Finger extensors
Scapuloperoneal muscular dystrophies	Unknown	Childhood-adulthood	Distal arms, Peroneal distribution
Oculopharyngodistal myopathy	Unknown	Adulthood	Facial, bulbar muscles Distal muscles

Table 3: Congenital Myopathies			
Name	**Gene**	**Inheritance**	**Clinical features**
Nemaline myopathy	Alpha-tropomyosin (TPM3), Nebulin (NEB), Alpha-actin (ACTA1), Beta-tropomyosin (TPM2), Troponin T (TNNT1), Actin-binding protein muscle cofilin-2 (CFL2)	AD, AR, Sporadic	Proximal or diffuse weakness, Static/slowly progressive, Respiratory insufficiency, Scoliosis, Acquired joint contractures
Central core disease	Ryanodine receptor (RYR1)	AD, AR, Sporadic	Proximal weakness, Static/slowly progressive Scoliosis, Congenital hip dislocation
Myotubular myopathy	Myotubularin (MTM1)	X-linked	Severe Weakness, Respiratory insufficiency (severe), Ptosis, ophthalmoplegia Macrocephaly
Centronuclear myopathy	Dynamin 2 (DNM2), Amphiphysin (BIN1)	AD, AR	Weakness variable, Ophthalmoplegia, Respiratory insufficiency (late onset)
Multiminicore myopathy	Selenoprotein N (SEPN1), Ryanodine receptor (RYR1)	AD, AR	Weakness moderate, Respiratory insufficiency (late onset), Ophthalmoplegia, Spinal rigidity, Cardiomyopathy
Congenital fiber-type disproportion	Selenoprotein N (SEPN1), Ryanodine receptor (RYR1), Alpha-tropomyosin (TPM3), Alpha-actin (ACTA1), Beta-tropomyosin (TPM2)	AD, AR, X-linked	Weakness variable, Respiratory insufficiency occasionally, Ophthalmoplegia, Scoliosis
Myofibrillar myopathy (MFM) (desmin-related myopathy, DRM)	αβ-crystallin (CRYAB), Desmin (DES), Myotilin (MYOT), Selenoprotein N (SEPN1)	AD, AR	Proximal or generalized weakness, Distal or generalized weakness, Cardiac arrhythmia or cardiomyopathy
Hyaline body myopathy (myosin storage myopathy)	Slow myosin heavy chain (MYH7)	AD, AR	Proximal or generalized weakness, Distal weakness

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Table 4: Congenital Muscular Dystrophies (CMD)		
Protein	**Clinical Phenotype**	**Clinical features** Unique to subtype
Merosin (lamin-α2) (LAMA2)	Merosin-deficient CMD (MDC1A)	White matter changes on MRI brain Demyelinating neuropathy
Collagen VI (COL6A1, A2, A3)	Ulrich CMD (AD) Bethlem CMD	Proximal contractures, Distal hyperextensibility, Sandpaper rash
Integrin α7 (ITGA7)	Merosin-positive CMD	Mental retardation
Plectin (PLEC1)	CMD with epidermolysis bullosa	Blistering rash (from birth)
Fukutin (FCMD)	Fukuyama CMD (FCMD) Walker-Warburg syndrome	Eye and brain structural anomalies Seizures, Mental retardation
Protein-O-mannose β1.2 N-acetylglucosaminyltransferase 1 (POMGnT1)	Muscle-eye-brain disease (MEB)	Eye and brain structural anomalies
Protein-O-mannosyltransferase 1 (POMT1)	Walker-Warburg syndrome (WWS) LGMD2K	Eye and brain structural anomalies Seizures, Mental retardation
Protein-O-mannosyltransferase 2 (POMT2)	Walker-Warburg syndrome Muscle-eye-brain disease	Hydrocephalus Brain structural anomalies (severe)
?	MDC1B	Muscle hypertrophy Respiratory failure (early)
Fukutin-related protein (FKRP)	LGMD2I MDC1C FCMD MEB WWS	Duchenne muscular dystrophy phenotype Cardiomyopathy
LARGE	MDC1D	Mental retardation (severe) White matter changes on MRI brain
SIL1	Marinesco-Sjogren syndrome	Cerebellar ataxia Congenital cataracts
Selenoprotein N (SEPN1)	Rigid Spine muscular dystrophy Multiminicore myopathy Congenital fiber-type disproportion Myofibrillar myopathy	Thin muscle bulk Spinal rigidity Respiratory insufficiency (early)
Lamin A/C (LMNA)	Emery-Dreifuss (AD and AR) LGMD1B (AD) CMD Dilated cardiomyopathy CMT2B1	Variable neuromuscular phenotypes

*Above dystrophies inherited in an autosomal recessive manner unless otherwise indicated.
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